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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,471	08/18/2000	Carol M. Kinoshita	10278-017001	6615

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,471	KINOSHITA ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/28/05, 10/13/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *105,106,109-131,133-142,144-164,167-171,184 and 185* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105,106,109-131,133-142,144-164,167-171,184 and 185* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/12/04; 10/13/04*; 11/1/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 13, 2004 has been entered.

The AF amendment field March 18, 2004 amending the specification to capitalize trademark names and to insert reference to US 5,641,670, canceling claims 81-104, 132, 143, 165, 166 and 172-183 and amending claims 144, 147 and 184 has been entered.

A complete list of all pending claims has been filed January 28, 2005.

Claims 105, 106, 109-131, 133-142, 144-164, 167-171, 184 and 185 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 141, 142 and 167-169 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 141 and 142 depend from claim 139 drawn to a method of use of a class I mannosidase inhibitor. Class I mannosidase inhibitor prevents the removal of α1,2 mannose residues. Claims 141 and 142 recite the limitation "wherein the mannosidase inhibitor prevents the removal one α1,3 mannose residues" or "α1,6 mannose residues", respectively. Since class I mannosidase inhibitor has different specificity, claims 141 and 142 are confusing.

Claims 167-169 are incomplete as dependent from canceled claim 166. in the interests of the compact prosecution claims 167-169 have been construed as dependent from claim 139.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 105, 106, 109-128, 130, 131, 133-138, 184 and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. in view of Smith et al.

Friedman et al. (US Patent 5,549,892, form P7-0-1449 filed November 30, 2000, reference AD) teach the importance of a glycoprotein, human GCB, needed for treatment of Gaucher's disease. They teach the importance of GCB remodeling for the production of a pharmaceutically effective preparation and the

encoding human GCB comprises exogenous regulatory and coding sequences (columns 3, 4). Friedman et al. teach that the remodeling of the carbohydrate chains may be accomplished by several different alternative ways such as utilizing mutant cell lines deficient in certain carbohydrate synthetic pathways (column 6, lines 1-15).

Smith et al. (US Patent 5,939,279) teach that growing eukaryotic cells in the presence of inhibitors of glycoprotein processing can alter N-linked oligosaccharides. They teach that two such inhibitors, deoxymannojirimycin and kifunensine, inhibit α-mannosidases that trim mannoses from $Man_9(GlcAc)_2$ (column 8, lines 4-15). They teach the method of preparing high mannose $Man_9(GlcAc)_2$ glycoproteins by treating human HT-29 cells with mannosidase I inhibitors, deoxymannojirimycin or kifunensine (columns 7-8, column 9, claim 8). With regard to claims 109 and 110, Smith et al. teach the required range of the kifunensine concentration (column 8, lines 24 and 25). With regard to claims 111-114, Smith et al. teach the required range of the swainsonine concentration (column 8, line 26). Therefore, *Smith et al. teach a general method of altering oligosaccharides attached to protein moiety in glycoproteins by growing human cells in the presence of inhibitors of glycoprotein processing*. They teach that the treatment of human HT-29 cells with kifunensine results in glycoproteins comprising $Man_9(GlcAc)_2$. One of such glycoproteins present in HT-29 cells is GCB.

Therefore, at the time the invention was made, the importance of remodeling GCB to produce hmGCB has been acknowledged. Remodeling by

Therefore, at the time the invention was made, the importance of remodeling GCB to produce hmGCB has been acknowledged. Remodeling by growing eukaryotic cells in the presence of inhibitors of glycoprotein processing has been known. The use of mannosidase inhibitors, such as kifunensine, as a tool for such remodeling to obtain $Man_9(GlcAc)_2$ oligosaccharide was known. The genetic manipulation of protein expression and techniques to make a knockout gene of a known structure and antisense molecule therefor were known.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to grow cells that whether recombinantly or naturally express GCB in the presence of mannosidase inhibitors in order to prepare hmGCB. Any human cell such as HT-29, for example, or a mammalian cell transformed with a DNA encoding human GCB such as CHO as taught by Friedman et al. or COS, can be employed.

One of ordinary skill in the ad at the time the invention was made would have been motivated to specifically purify GCB in view of its pharmaceutical importance taught by Friedman et al. The high expectation of success is provided by Smith et al. who teach the requisite step for preparing remodeled glycoproteins. The purification of proteins from the cells is standard in the art and is taught by Friedman et al., for example.

Claims 129, 139-142, 144-164 and 167-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Treco et al. in view of Smith et al. and further in view of Friedman et al.

Treco et al (US Patent 6,270,989) teach that in many cases, it is desirable to produce human therapeutic proteins in human cell, for example, when it is desired that the glycosylation pattern of the protein be similar to patterns normally found on human cells (column 3, lines 6-15). They teach the production of a pharmaceutically useful preparations of various proteins using gene activated endogenous genes encoding said proteins (abstract). They teach various human cells that can be used for the production of the endogenous proteins (e.g., claim 97). They teach the production of GCB (gene-activated GCB) using HT1080 cells (claims 324, 332).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to grow human cells producing GCB in the presence of mannosidase inhibitors in order to generate hmGCB. It would have been further obvious to use human cells producing GA-GCB because they produce a greater amount of the desired protein as compared to the cells before gene activation.

Friedman provides motivation for the production a pharmaceutically effective preparation of a human GCB wherein its carbohydrate chains are remodeled. Smith provides tools to obtain the desired carbohydrate structure by growing the cells expressing GCB in presence of mannosidase inhibitors.

Response to Arguments

Applicant's arguments filed March 18, 2004 have been fully considered but they are not persuasive.

Applicants argue that "Smith has nothing to do with GCB. There is no suggestion or motivation in Smith to harvest any protein, much less a specific protein such as GCB, from the HT29 cells. The Examiner argues that motivation to harvest GCB expressed by the HT-29 cells of Smith is provided by Friedman's teaching of the importance of carbohydrate remodeling in GCB function. The Examiner concludes: "Therefore, there is motivation to obtain a hmGCB by known means. Kifunensine is one of such well known means used in remodeling." As the Examiner acknowledges, kifunensine is merely one of many methods used in carbohydrate remodeling. However, the fact that it may be desirable or important to produce high mannose GCB does not make any one particular method of doing so obvious, particularly when many other alternatives exist. Indeed, Friedman (which relates specifically to GCB) lists several types of methods for carbohydrate remodeling, including using mutant cell lines deficient in certain carbohydrate synthetic pathways and chemical modification of the oligosaccharide of the purified recombinant GCB. Friedman does not suggest using any mannosidase inhibitor. Thus, the Examiner has not addressed the substance of Applicants' argument that, without using the claims as a template, it would have been impossible to choose kifunensine from the large group of known carbohydrate modifiers, to combine with Friedman. Applicants maintain that the Examiner has used hindsight to pick and choose the elements of the claims from the art. This is impermissible. Accordingly, a prima face case of obviousness has not been made " (Remarks, page 16).

It is not agreed with that "Smith has nothing to do with GCB". Smith teaches the method of obtaining the glycoprotein comprising the desired oligosaccharide such as $Man_9(GlcAc)_2$ by growing human cells in the presence of mannosidase inhibitors. GCB is present in these cells and therefore, is among the proteins comprising said oligosaccharide moiety. Friedman et al teach that carbohydrate chains of GCB should be altered in order for GCB to be therapeutically effective. Smith provides a method for the desired remodeling. Neither of the references teaches the same invention as the claimed by Applicants. However, as the references in the 103(a) rejection, these references do not have to disclose the same invention but only to make it obvious. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants further argue that "In response to Applicants' arguments regarding surprising results, discussed in the Reply filed July 14, 2003, the Examiner argues that Applicants' showing of an approximately 4-fold increase in GCB uptake was not unexpected in view of Furbish et al. (BBA, 1981, 673:425-434), which discloses that isolated GCB treated with various glycosidases

showed a 5-fold increase in uptake. Applicants strongly disagree that Furbish et al. provides the proper basis for comparison for Applicants' results. Treating an isolated glycoprotein directly with a glycosidase to remodel the oligosaccharide structure of the glycoprotein (as taught by Furbish) is a completely different type of carbohydrate remodeling method than treating a cell with a glycosidase inhibitor (in this case, a mannosidase inhibitor), as claimed. The Furbish method directly exposes an isolated glycoprotein to an oligosaccharide-remodeling enzyme and can thus be expected to be very efficient. Because a mannosidase inhibitor acts to inhibit an enzyme in the N-terminal glycosylation pathway during glycoprotein synthesis in the cell, it affects the oligosaccharide composition of glycoproteins indirectly. Thus, even if a skilled artisan had been motivated to try the claimed methods (which of course is not sufficient for a prima case of obviousness), the claimed method would have been expected to be inefficient compared to the direct, glycosidase remodeling method of Furbish. As such, the fact that the claimed method results in approximately the same level of increase in uptake as Furbish is, by itself, surprising. Indeed, Smith suggests that at most, one could expect a 50-75% change in a functional aspect of a glycoprotein expressed from a kifunensine treated cell. That is, Smith teaches that "the receptor molecule on the bacteria recognizes high-mannose oligosaccharides on the HT-29 cell surface" (Smith 7:27-30). However, treating a cell with either kifunensine or deoxymannojirimycin increased the number of radioactive bacteria bound to HT-29 cells by only 50-75 % (Smith 8:32-35). Therefore, in view of Smith, Applicants' results showing that GCB harvested from kifunensine treated

cells showed a 400 % increase in function (e.g., uptake) is indeed unexpected. Accordingly, even if a prima facie case of obviousness had been made (which Applicants do not concede), Applicants' unexpected results are sufficient to overcome it" (pages 16-17).

These arguments are not persuasive because if comparing the instant results with Furbish is improper, more so is comparing them with Smith.

Smith measures the adhesion of bacterial *E. cloacae* cells to human HT-29 cells that is not the same as to measure directly the GCB activity in a cell lysate. Furthermore while the absolute uptake of GA-GCB produced by kifunensine treated HT1080 cells in mouse J774E cells is increased about 4-fold (400%), the mannose receptor specific uptake measured in the presence of mannan increased about 2-fold (Table 2, page 54). It appears to be not surprising that after the treatment with an inhibitor, kifunensine, that prevents the trimming of mannose, the uptake by mannose receptor is increased 2-fold.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

April 14, 2005